REMARKS

Claims 1 and 3-6 are pending. The current set of claims is in the January 9, 2009 Amendment.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Prior Art Based Issues

The following prior art based rejections are pending:

> (A) Claims 1, 3 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Tabata et al. (Advanced Drug Delivery Reviews 31 (1998) 287-301).
> (B) Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tabata et al. in view of Ueda et al. (US 4,749,574).

Applicant respectfully traverses, and reconsideration and withdrawal of these rejections are respectfully requested.

There are currently two independent claims, which are claims 1 and 3. Claim 1 is drawn to a sustained-release preparation and claim 3 is drawn to a method of sustained release of a drug in vivo. The features of claims 1 and 3 are as follows:

> **1**. A sustained-release preparation which comprises a drug and a gelatin hydrogel,
>
> wherein the drug is impregnated into said gelatin hydrogel through a surface thereof and is maintained in said hydrogel by physiochemical interaction, and
>
> wherein a concentration gradient of the drug is formed in the hydrogel, ***said concentration gradient being higher at said surface than in other parts of said hydrogel***, and
>
> said sustained-release preparation is sterile.

3. A method of sustained release of a drug in vivo comprising

administering a sustained-release preparation to a patient in need thereof,

said preparation comprising a drug and a gelatin hydrogel, wherein a concentration gradient of the drug is formed in the hydrogel,

wherein degradation of the gelatin hydrogel *in vivo* causes more drug to be released from a region with higher drug concentration, thereby giving said sustained release of the drug,

wherein the drug is impregnated into said gelatin hydrogel through a surface thereof and is maintained in said hydrogel by physiochemical interaction, said ***concentration gradient being higher at said surface than in other parts of said hydrogel***, and

said sustained-release preparation is sterile.

Applicant respectfully submits that Tabata et al., either taken alone, or in combination with Ueda et al., fail to teach or fairly suggest all of the features of the presently claimed sustained release preparation of claim 1 or the method of claim 3. For example, it is clear that Tabata et al. fail to teach or suggest a concentration gradient of the drug. On this point, the Examiner states as follows:

> The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface.

The Examiner appears to be taking "Official Notice" of several facts which are unsupported by documentary evidence. MPEP 2144.03 gives instructions on when Official Notice unsupported by documentary evidence is appropriate. MPEP 2144.03 states:

> Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known.

First, the Examiner appears to take Official Notice of the fact that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation. It is unclear to Applicant what basis the Examiner has for making this statement. Applicant respectfully challenges this first assertion by the Examiner. Applicant requests that the Examiner provides documentary evidence to support the assertion that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation.

Second, the Examiner appears to take Official Notice of the fact that the concentration of the drug will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel. Again, Applicant respectfully challenges this second assertion by the Examiner. Applicant requests that the Examiner provides documentary evidence to support the assertion that the concentration of the drug will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel.

Furthermore, if it is the Examiner's position that a *prima facie* case of anticipation is present in view of the fact that the concentration gradient would be **inherent** in the hydrogel of Tabata et al., Applicant respectfully disagrees. In order for the Examiner to set forth a *prima facie case*, there must be sufficient evidence in the cited reference to assert that the missing feature of the claimed invention is actually in the product of the prior art. To support an anticipation rejection based upon inherency, an Examiner must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the prior art.

See *Ex parte Levy* 17 USPQ2d 1461 (BOPAI 1990); see also *In re Oelrich*, 212 USPQ 323 (CCPA 1981) holding that inherency must flow as a necessary conclusion from the prior art, not simply a possible one. Here, we do not believe that the cited reference provides any disclosure which would make one skilled in the art believe that the concentration gradient would necessarily be **inherent** in the hydrogel of Tabata et al.

Although it is unclear to Applicant what the basis for the Examiner's belief is, Applicant guesses that the Examiner believes that the discussion of "sorption" of the protein relates to surface adsorption. However, this is not the case. For example, the Examiner's attention is drawn to Section 3.2 of Tabata et al. titled "Interaction of protein with gelatin hydrogels" beginning on page 292. The Examiner will note that Tabata et al. state: "the interaction of protein with gelatin results in protein sorption to the gelatin hydrogel." At the top of the second column on page 292, Tabata et al. state that the bFGF protein molecules "***freely diffuse into the interior*** of the hydrogels." (Emphasis added). Applicant respectfully submits that the skilled artisan would not reasonably conclude that protein molecules which freely diffuse into the interior of a hydrogel would have a concentration gradient with a higher concentration at the surface.

Although Applicant's examples in the present specification are not limiting of the invention, the Examiner will note that the examples in the present specification describe a method of forming the sustained-release preparation which is very different from the method discussed in Tabata et al. As such, it is unclear to Applicant the basis for the Examiner's assertion that *prima facie* case of anticipation is present in view of the fact that the concentration gradient would be **inherent** in the hydrogel of Tabata et al.

Tabata et al discloses that protein drug complexed with gelatin hydrogel is released as a result of its biodegradation, but does not at all teach or suggest "concentration gradient" of the protein. The Examiner merely conjectures that the concentration gradient will be generated when the hydrogel is biodegraded or when a protein is applied to the hydrogel.

As such, clear patentable distinctions exist between the present invention and the teachings of Tabata et al. and a *prima facie* case of anticipation cannot be said to exist.

In addition, the Examiner cites Ueda et al. in order to cure deficiencies in Tabata et al. with respect to present claim 4. In view of the fact that Ueda et al. fail to cure the deficiencies of Tabata et al., a *prima facie* case of obviousness cannot be said to exist.

Based on the remarks herein, reconsideration and withdrawal of all rejections are respectfully requested.

Conclusion

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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